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Machine Perfusion of Donor Livers for Transplantation: A Proposal for Standardized Nomenclature and Reporting Guidelines

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Running Title: Standardization of nomenclature and reporting of liver machine perfusion

Abbreviations:

MP- Machine perfusion, SCS – static cold storage, PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

ABSTRACT

With increasing demand for donor organs for transplantation, machine perfusion promises to be a beneficial alternative preservation method for donor livers; particularly those considered to be of sub-optimal quality, also known as extended criteria donor livers. Over the last decade, numerous studies researching MP of donor livers have been published and incredible advances have been made both in experimental and clinical research in this area. With numerous research groups working on MP, various techniques are being explored, often applying different nomenclature. The objective of this review is to catalog the

differences observed in the nomenclature used in the current literature to denote various MP techniques and in the manner in which methodology is reported. From this analysis, we propose a standardization of nomenclature on liver MP to maximize consistency, enable reliable comparison and meta-analyses of studies. In addition, we propose a standardized set of guidelines for the reporting of methodology of future studies on liver MP which will facilitate comparison as well as clinical implementation of liver MP procedures.

INTRODUCTION

In an effort to meet the demand for donor organs needed for transplantation, livers considered to be of sub-optimal quality and function are increasingly being transplanted. Given the increased vulnerability of these organs and the potential injury incurred during procurement and storage/transportation, machine perfusion (MP) is a promising alternative to static cold storage (SCS); the current standard of care in donor liver preservation. Following the first successful series of extra-corporeally perfused canine liver grafts performed by Brettschneider and Starzl et al in 1967 (1), machine perfusion has been explored as a method to achieve preservation of donor livers under conditions simulating normal *in-vivo* physiology in an attempt to minimize ischemia-related injury associated with static cold storage. Research into MP has established three major benefits; the capability to preserve donor organs whilst providing them with oxygen and nutrients at various temperatures (optimal and prolonged preservation), the ability to re-condition and optimize the function of donor organs, particularly extended criteria organs, with for instance oxygen perfsufflation, de-fatting techniques for steatotic livers and pharmaceutical intervention (organ resuscitation and function recovery); and lastly, machine perfusion, at 37˚C, provides the possibility of testing the function and viability of the organ prior to transplantation (*ex-situ* viability testing).

With the number of publications on liver MP to date exceeding 500, the last 10 years has seen an incredible advancement in both experimental and clinical research into donor liver MP. Several groups have been exploring different methods of MP with the major technique differences relating to the temperatures used, the provision of oxygen and whether the technique is flow or pressure controlled. Given that MP is a nascent technology with many technical aspects continuing to be explored, adapted and improved, the publications on MP have exhibited great discrepancies. These include the nomenclature used to describe the different MP techniques (abbreviations included), the temperatures considered to be hypo-, subnormo- or normothermic and the manner in which certain details of the methodology are reported. The absence of standardized nomenclature and guidelines for the reporting of technical details pertaining to MP gives rise to the relatively large variation that exists among studies. This makes it difficult to compare different studies, perform meta-analyses and in some cases, attempt to re-execute the methodology used.

With the number of clinical studies on MP of donor livers rapidly increasing, it is of importance that a consensus is reached on the nomenclature applied and on what necessary aspects of the methodology should be included in a paper. The objective of this review is to catalog the differences observed in the nomenclature used in the current literature to denote various techniques of liver MP and in the manner in which the methodology is described. From our analysis, we aim to address these discrepancies and propose recommendations for nomenclature and develop a standardized set of guidelines for reporting methodology for future studies on MP of donor livers.

METHODS

Literature search strategy

A comprehensive literature search for all published articles regarding machine perfusion of donor livers was performed using the PubMed, EMBASE, MEDLINE, Web of Science and The Cochrane Library databases. The final date of the search was the 17th of February 2015. In order to ensure all potentially relevant articles were included in the search, no

specific date limits were set. The search was conducted using the medical subject heading (MeSH) terms and Emtree key words “machine perfusion, machine preservation, liver transplantation, hepatic transplantation” combined with free text terms regarding machine perfusion of donor livers such as “hypothermic”, “normothermic”, “subnormothermic” etc.

Selection criteria and data collection

Study selection was performed independently by two authors (S.A.K and R.J.P) in a standardized fashion using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method (2). Study inclusion was carried out in three phases; an initial title search was carried out whereby relevant titles were screened and studies whose titles were unrelated to the aims of this review were excluded. The abstracts of the remaining studies were then acquired and independently assessed for eligibility. Full papers of the abstracts regarded as potentially eligible were retrieved and underwent complete review and assessment until a final compilation of articles was made. For articles where an inconsistency between the two authors occurred, a discussion about these articles was held in order to reach to a consensus. **Figure 1** illustrates the study selection procedure and the inclusion and exclusion criteria.

Inclusion criteria

- All articles on machine perfusion of donor livers
- Fully accessible articles written in English and published in scientific journals
- Human & animal studies

Exclusion criteria

- Irrelevant to title and objective of review
- Non-English
- Articles about machine perfusion of other organs
- Full version inaccessible

Data extraction and analysis

The data from the included studies was assessed, with the main focus of these articles being the *materials and methods* section. The primary aim of this study was to investigate the manner in which the methodology of these studies was reported and to determine how certain aspects concerning the MP procedure were mentioned. The recommendations and guidelines that this review provides were extensively discussed and agreed upon by all authors of this paper.

RESULTS

Of the 2,265 articles identified from the initial literature search, 127 of these ultimately met all inclusion criteria. (**Figure 1**) These papers were published between 1997 and 2015 and constituted both animal and human clinical studies. From our analyses, we observed several differences in the manner in which the same type of machine perfusion techniques were referred to as well as marked variation in the temperatures used. In the paragraphs and tables below, we highlight and assess these differences as well as provide recommendations to establish uniformity in the manner in which data are reported.

1. Timing of Machine Perfusion

In all the studies reviewed in this paper, MP was conducted either for (almost) the entire duration of preservation phase of the transplantation process, or before or after a period of traditional SCS. A significant majority of the research groups whose studies included animal studies (3-34) and studies at which the donor and recipient center were the same location (35) nearly totally eliminated the SCS phase; thus perfusing donor organs immediately after procurement until the point of implantation. The rest of the studies; particularly most human studies, performed MP for various time periods after a few hours of SCS (during transport of the organs from the donor to recipient centers) or as a result of prolonged cold ischemia times due to various logistical or unforeseen circumstances.(36-50) Interesting to note, as opposed to performing MP for the entire preservation phase, the first clinical studies

conducted by Guarrera et al and Dutkowski et al chose to focus on exclusively conducting MP after a period of traditional SCS and immediately prior to implantation (< 2 hours prior).(35,40,45,46,51)

2. Nomenclature and Abbreviations Used to Identify the Type of Machine Perfusion

As the pioneering technique of MP, a number of different terms, as shown in **Table 1** below, have been used to describe hypothermic MP in the past two decades. Even though the majority of the studies mention the term "hypothermic" within the title and/or article itself, a number of papers simply use the term *machine perfusion*; without specific indication of the temperature used. Other types of MP include "subnormothermic" and "normothermic" perfusion. For all three major types of MP, despite referring to the same procedure, numerous abbreviations are used to describe the type of MP performed (**Table 1***)*.

Additionally, for subnormothermic and normothermic MP, a major difference lay in the additional emphasis of whether these perfusions were performed extra corporeally or not.

3. Temperatures used during machine perfusion

Although, in general, three types of MP can be recognized (i.e. hypothermic, subnormothermic and normothermic), we noted marked inconsistency in the actual temperatures denoted by these terms. The following findings are summarized in (**Table 2**). A number of papers (7,15,52,53), despite including a description of the technique of MP, fail to specify what particular temperatures were used in their respective studies whilst some descriptions use arbitrary and unspecific terms such as "warm", "cold" or "room temperature" (23,33,39,54,55) to denote the temperatures used during MP. Twenty-six of the 58 (45%) studies on hypothermic MP reported perfusing the livers at 4°C whereas the rest perform MP at different temperatures within the 0 – 10°C range. All studies on subnormothermic MP were generally conducted at temperatures between 20 and 30°C. However, the majority of these studies reported using 20°C or 21°C which in all cases was what the authors referred

to as being room temperature. Normothermic MP was primarily carried out at the physiological body temperature of humans or the animal of study although small discrepancies were seen in the temperatures stated as being the physiological body temperature of the different animals.

3. *Other aspects of methodology*

In addition to the discrepancies in temperature, analysis of the literature exhibited variation in the description of certain technical aspects of the machine perfusion procedure. For instance, seven studies lack a clear description of whether the liver underwent single (via the hepatic artery or portal vein) or dual perfusion.(16,23,24,56-59) As opposed to the vast majority (92%) of the studies which stipulated whether they made use of a pressure or flow controlled system and provided specifications of the settings they used, a number of studies fail to specify this.(7,12,16,24,56,59-65) All studies that provided oxygenation during MP explicitly stated this in the methodology, however a number of studies went further to specifically outline the details such as the O_2/CO_2 mixture or the oxygen tension (2,3,5,6,44,64-67,71-73,76,84,99,100,101,108,119,123) as opposed to simply mentioning the presence of an oxygenator within the MP system.(6,11,18,20,22,24,59,60,62,64-71) Lastly, a significant number of the studies also clearly mentioned the type of pump used during MP (2,3,5,6,26,64-67,72-74,76,84,99-101,108,119,120,123,127), which gives an indication of the flow pattern through the liver.

DISCUSSION

In an effort to initiate and facilitate a standardization of nomenclature as well as to establish guidelines on the experimental and clinical reporting of machine perfusion of donor livers, this systematic literature review assessed the differences in the nomenclature, temperatures and techniques currently used and reported in published articles.

1. *The Timing of Machine Perfusion*

Given that the timing and duration of MP during the entire preservation and transportation period is essentially correlated to the specific benefits MP is intended to provide to the organ, it is important that the period at which MP is performed is specified; for instance, organ reconditioning and optimization can be applied either prior to or after static cold storage whereas viability testing is generally performed shortly before implantation.

It is evident from the reviewed literature that machine perfusion can be performed mainly at three particular time points; (1) immediately after organ procurement, before the organ is stored on ice for transportation (pre-static cold storage), (2) (shortly) before organ implantation, especially in instances with longer cold ischemia times (post-static cold storage) and (3) for the entire preservation period between procurement and implantation, thus (nearly) eliminating the need for SCS. In the case of the latter method, we propose the term “preservation MP”. When applying preservation MP, a short period of SCS is still required during and immediately after organ procurement, when the organ is prepared for connection to the perfusion device, and shortly before implantation to avoid warm ischemia during the anastomosis time. We thus propose to use the term preservation MP when the time period of SCS either before or after MP is less than a *maximum* of 3 hours (**Figure 2**). This 3 hour time frame is based on the experience of the authors of this paper with various techniques of machine perfusion. It was generally agreed that in reality it normally takes approximately 1.5 to 2 hours from the point of in-situ cold flush, donor hepatectomy, back table procedure to connection of the organ onto the perfusion device. However, there are a number of cases in which this may be delayed; for example in livers with aberrant arterial vasculature which requires vascular reconstructions and thus extra back table time is needed before the liver can be connected to the device. This 3 hour time frame is therefore the recommended maximum time period that allows for unavoidable circumstances that may cause a delay before machine perfusion can be started. Similarly, it generally takes 40-60 min to make the vascular anastomoses in the recipient until reperfusion can be initiated.

When this is added to the time needed to take a donor liver off the machine, flush out machine perfusion fluid, remove the cannula's and perform the last back table work (i.e. trimming of vessels and preparation of the venacava in the donor for piggy back anastomosis), one may expect a total time period of 1-3 hours before graft reperfusion in the recipient occurs. Therefore this 3 hours of SCS reflect a maximum time period. If the duration of SCS is longer than 3 hours and MP is applied either prior (immediately after procurement) or after SCS (short before implantation), we propose to call this "pre-SCS MP" and "post SCS MP", respectively.

2. Nomenclature and Abbreviations

A number of different terms and abbreviations have been used in the observed studies describing generally similar MP methods. In some of these cases, a few aspects such as oxygenation or single/dual perfusion may have differed and were incorporated. In order to minimize confusion and tackle the heterogeneity in the nomenclature, we believe that authors of future publications should avoid adapting other aspects of perfusion into the nomenclature and retain simplicity. Given the importance of specifying certain aspects of MP performed, the choice to use certain terms in the title and throughout the publication remains within the discretion of the author although it is advised that the use of the standardized abbreviations for the respective types of MP; HMP (hypothermic machine perfusion), MMP (mid-thermic machine perfusion), SMP (sub-normothermic machine perfusion), and NMP (normothermic machine perfusion) be maintained.

3. *Temperature Ranges*

As described in the Results section, experiments conducted on MP of donor livers have generally been performed at three temperature ranges; hypothermically at 0-10˚C, sub-normothermically at 20-33˚C and normothermically at 35-38˚C (depending on the species used in study). Based on common practice of the various research groups working on liver

MP and following a discussion with the authors involved in this review, the following classification of the standardized temperature ranges is proposed.

Hypothermic MP (0 – 12˚C)

All studies involving hypothermic MP so far have been conducted at temperatures of 10˚C and below with the major reason being that the rate of metabolism and enzymatic reactions in mammalian cells decreases to rates as low as 20% or even less (128,129) (**Figure 3**). The benefit of HMP is that it minimizes preservation injury whilst improving organ viability and for oxygenated livers, replenishes adenosine tri-phosphate (ATP) stores. The reason for proposing 12˚C as the cut-off point for hypothermic MP is because the rates of numerous energy dependent reactions of liver mitochondrial enzymes exhibit a significant change at 12.5˚C. (130)

Midthermic MP (13 – 24˚C) and Subnormothermic MP (25 – 34˚C)

The term *subnormothermic* has been considered for temperature ranges varying between 12˚C and 35˚C even though in the majority of studies in which the temperature was referred to as subnormothermic, MP was performed at 20-22 ˚C. This broad temperature range shows a great difference in the rate of metabolism at, for example 12˚C as compared to 33˚C (**Figure 2**). Furthermore, it can be argued that temperatures as low as 15, 18 or 20 ˚C are too low to be considered as *subnormothermic* as not only does this term suggest being slightly below normal body temperature, but at such low temperatures a living person would be defined as (extremely) hypothermic. Whereas at higher temperatures such as 30-33˚C, the rate of metabolism increases close to 70% of the normal rate at body temperature (**Figure 3**). Based on this, we propose to use the term *mid-thermic* (13 – 24˚C) to distinguish the lower temperatures (0–12˚C) from the less physiologically abnormal subnormothermic temperature range (25-34˚C).

Normothermic MP (35 - 38˚C)

The term *normothermic* should refer to the normal core body temperature of the species used in the study, i.e. 37˚C for human and rodent studies and 38˚C in studies with porcine models.

4. *Ex-vivo or Ex-situ MP*

An additional aspect of MP that demonstrated particular variation in the literature was the referral of MP as being performed "*ex-vivo*" or "*ex-situ*". Given that MP involves perfusion of donor livers outside the body of a deceased donor, the term "*ex- vivo"* which, refers to "outside of the living body", does not seem appropriate. Therefore, the term "*ex-situ",* which refers to "outside original location/position", is proposed as a more representative description of what occurs during MP.

Other Technical Aspects and Reporting Guidelines

Along with discrepancies in the nomenclature and temperature ranges, reporting of other aspects, particularly technical aspects belonging to methodology were observed. Given the ongoing advancement in the field of MP, it is important that certain methodological aspects are explicitly stated to ensure that studies can be reproduced as well as objectively compared with each other. Moreover, with more clinical trials currently being performed, this will facilitate future meta-analyses with maximum validity and reliability. The authors of this review reached a consensus on various aspects of the MP procedure that were considered fundamental and developed a checklist that can be utilized and referred to when preparing a report on liver MP (**Table 3**). Important aspects in this checklist include clear descriptions of the flushing technique, all the technical aspects of the MP procedure, type of perfusion fluid used, and clarification of the time point, duration and temperatures at which MP is conducted. Furthermore, in order to make valid comparisons of experimental outcomes, the manner in which data is presented and described, particularly in the *results* section of publications, is important. The selection of (clinically) relevant endpoints during machine

perfusion was not the objective of this paper but the reader is referred to other recent reviews that have summarized the various types of biomarkers that can be used during MP for graft viability assessment (72,73). Naturally, in clinical trials traditional outcome parameters such as graft and patient survival rates, as well as hepatic and systemic postoperative complications will be relevant endpoints. In case of DCD liver transplantation, a major clinical endpoint should be the incidence of postoperative biliary complications.

CONCLUSION

As experimental and clinical research into MP of donor livers advances, a standardization of nomenclature and reporting of technical aspects of MP is required to minimize heterogeneity and to facilitate more reliable and valid comparison analyses of studies. We hope this paper provides a useful overview on current nomenclature and will be helpful in reporting of future research studies on liver MP.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

FIGURE LEGENDS

Figure 1. Flow chart illustrating study selection and inclusion procedure. Irrelevant titles included studies mainly involving *in-vivo* perfusion (and not machine perfusion), *in-vitro* cell studies, follow-up studies on machine perfusion or studies involving analysis of data from studies on machine perfusion of donor livers without including the machine perfusion procedure description in the methodology.

Figure 2. Charts illustrating classification of the timing of machine perfusion. Machine perfusion (MP) conducted within 3 hours of organ procurement and followed by a period of static cold storage (SCS) is considered as Pre-SCS MP, whereas that performed after a period of at least 3 hours of SCS preservation prior to implantation as Post-SCS MP. Additionally, MP can be performed between periods of SCS. Duration of SCS and Preservation MP conducted within the 3 hour windows on either end of the procedure remains unspecified and can be widely varied. Lastly MP can also be performed for the entire preservation period (immediately after organ procurement until just before implantation).

Figure 3. Graphic presentation of the change in the rate of metabolism with decreasing temperature. Based on Van't Hoff's principle (expressed as $Q_{10} = (k_2 / k_1)^{10/(t_2 - t_1)}$), this graph demonstrates the significantly reduced metabolism at hypothermic temperatures (0 -12˚C). The vertical lines in the graphs indicate the lower endpoint of temperature ranges of the different types of MP proposed. Abbreviations: NMP; normothermic machine perfusion (35-38˚C); SMP, subnormothermic machine perfusion (25-34˚C); MMP, mid-thermic machine perfusion (13-24˚C); HMP, hypothermic machine perfusion (0-12˚C)

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Table 1. Nomenclature and abbreviations currently used for the different types of liver machine perfusion

Type of Machine Perfusion	**References**
Hypothermic (oxygenated) machine perfusion (HMP)	(1-8) (6,7,15,22,24,26,30,31,35,41-46,48-50,56,69,74-88)
Hypothermic oxygenated perfusion (HOPE)	(8,9,13,34,51,61,89-96)
Continuous Hypothermic Oxygenated Machine Perfusion (CHOP)	(97)
Machine perfusion (MP) or Machine Perfusion Preservation (MPP)	(53,57,63,64,98-103)
Cold Perfusion	(23)

Subnormothermic machine perfusion (SMP)	(11,104)
Subnormothermic machine perfusion (SNMP)	(3,10,18,39,105-108)
Subnormothermic ex-vivo liverperfusion (SNEVLP)	(17)
Subnormothermic machine perfusion (MP20)	(60,65-67,109-111)
Normothermic machine perfusion (NMP)	(16,19,21,25,29,36-38,40,62,70,71,112-116)
Normothermic extracorporeal perfusion (NELP)	(12,14,117-119)
Normothermic extracorporeal perfusion (NECMO)	(120)
Normothermic ex-vivo liver perfusion (NEVLP)	(5)
Warm perfusion	(33,54,55,62)

Table 2. Various temperatures currently used for the different types of liver machine perfusion

Hypothermic temperatures	**References**
0 - 4° C	(121)
1 - 3° C	(122)
2 ± 1° C	112
3 - 5° C	50
3 – 6° C	47,48
4° C	4,(8,50,53,89,100-103,123)
4 - 6° C	27,29,30,41,63
4 - 8° C	12,21,63
5° C	114
5 - 8° C	115-118
8° C	60,61
8 - 10° C	119
10° C	24,49,53-57,120,121
Subnormothermic temperatures	
20°C	69-71,81,83,85,114,122
21°C	11,72-75,77,123,124
25°C	76
33°C	78
20° - 30° C	82
Normothermic temperatures	
Porcine 38°C	89,90,95,109
Human 35.5 – 37.5°C	108
Rat 36.5 – 37°C	125
Human/rabbit/rat 37°C	9,52,91-94,100-102,106,126
Rat 37.5°C	(14,114,118)
(porcine) 39°C	86
“Warm”	8,96,97,127

Table 3. Checklist with recommended guidelines for reporting of relevant aspects of the methodology used in liver machine perfusion

1. Phase of preservation	• Timing ➢ Pre-SCS MP ➢ Preservation MP ➢ Post-SCS MP • Duration of MP ➢ Specified in hours/ minutes
2. Environment and Temperature	• *In situ* ➢ (Normothermic) Regional perfusion • *Ex situ*: ➢ Hypothermic MP (0 – 12°C) ➢ Midthermic MP (13 – 24°C) ➢ Subnormothermic MP (25 – 34°C) ➢ Normothermic MP (35 – 38°C)
3. Technical aspects	• Single or dual vessel perfusion (hepatic artery/ portal vein) ➢ Continuous or pulsatile flow • Pressure or flow controlled perfusion ➢ Computerized or manually controlled system • Perfusion temperature ➢ Specify temperature in °C ➢ Specify any significant temperature changes during MP (e.g. gradual rewarming) • Temperature control ➢ Automated or manual • Type of pump ➢ Roller / centrifugal / peristaltic
4. Perfusion fluid composition and oxygenation	• Perfusion fluid components ➢ Full description of the composition of the perfusion fluid used* • Oxygenation ➢ Ambient air, pure (100%) oxygen, or carbogen, other mixture • Heparin, antibiotics and nutrients

	• Any other interventions e.g. drugs etc.
5. Pre- and Post-MP phase	• Is organ flushed before and/or after MP? ➢ Which fluid is used and how much? ➢ At what temperature? • Specify vessels used in flushing of the organ

*Both at baseline as well as compounds that are continuously or intermittently administered during perfusion.

Figure 1

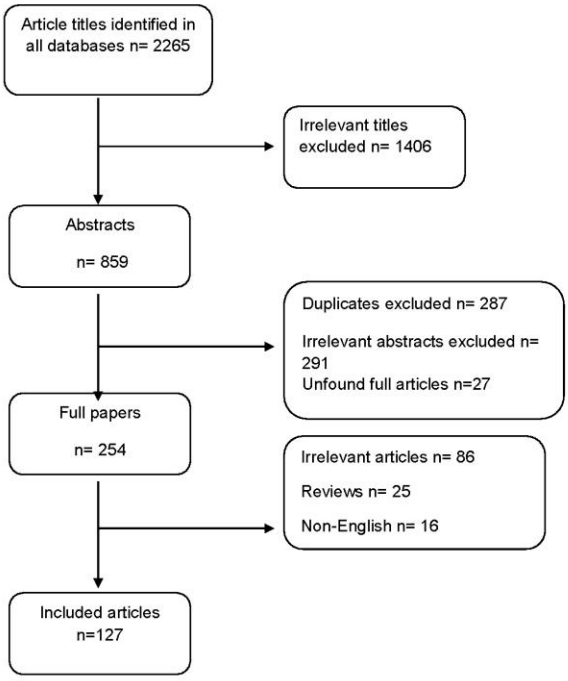

Figure 2

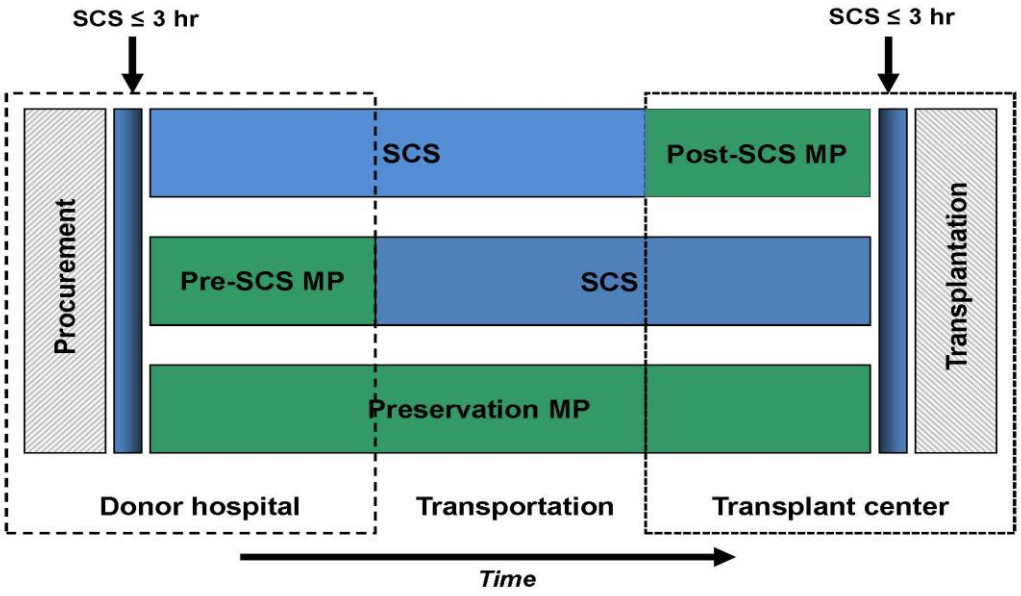

Figure 3